Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UKPAR

Potassium Chloride 0.4mmol/mL Solution for Infusion

(potassium chloride)

UK Licence No: PL 40739/0044

Ennogen Healthcare Limited

LAY SUMMARY

Potassium Chloride 0.4mmol/mL Solution for Infusion
(potassium chloride)

This is a summary of the Public Assessment Report (PAR) for Potassium Chloride 0.4mmol/mL Solution for Infusion (PL 40739/0044). It explains how Potassium Chloride 0.4mmol/mL Solution for Infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Potassium Chloride 0.4mmol/mL Solution for Infusion.

For ease of reading the product will be referred to as Potassium Chloride Solution for Infusion throughout the remainder of the lay summary.

For practical information about using Potassium Chloride Solution for Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

What is Potassium Chloride Solution for Infusion and what is it used for?
Potassium Chloride Solution for Infusion is a 'hybrid medicine'. It is similar to a 'reference medicine' containing the same active substance, but is available as a different strength, pharmaceutical form and has a different route of administration. The reference medicine for Potassium Chloride Solution for Infusion is Potassium Chloride 15% w/v Concentrate for Solution for Infusion (Mercury Pharma International Limited).

Potassium Chloride Solution for Infusion is used in patients needing additional amounts of potassium. Potassium helps the muscles, heart and other organs to work properly. Without the right amount of potassium the heart may start beat abnormally, which could be life-threatening.

How does Potassium Chloride Solution for Infusion work?
Potassium Chloride Solution for Infusion belongs to a group of medicines called electrolyte replacement solutions. Electrolytes are a group of chemicals and salts that are in body fluids, and they help to keep the water levels in different parts of the body in the right balance.

How is Potassium Chloride Solution for Infusion used?
The pharmaceutical form of this medicine is a solution for infusion and the product should only be administered by slow infusion via a central venous route.

Potassium Chloride Solution for Infusion will be given by a doctor or nurse. It will be slowly dripped through a needle into a vein (the doctor or nurse may call this an IV or intravenous infusion). This product is only for use via a central venous route.

The process may take an hour or more depending on the dose. The patient's doctor will decide on the best dose for their patient. The doctor will monitor the patient's heart while he/she receives the medicine. The doctor will also test the blood and check how much urine is produced by their patient.

Dose:
Adults and the elderly: The usual dose is up to 80mmol per day.

Infants and children: The usual dose is up to 3mmol per kg of bodyweight per day. For children weighing 25kg or over, refer to the adult dosage.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Potassium Chloride Solution for Infusion have been shown in studies?
No additional studies were needed as Potassium Chloride Solution for Infusion is a 'hybrid medicine' that is given as an aqueous intravenous solution and contains the same active substance as the reference medicine Potassium Chloride 15% w/v Concentrate for Solution for Infusion (Mercury Pharma International Limited).

What are the possible side effects of Potassium Chloride Solution for Infusion?
Because Potassium Chloride Solution for Infusion is a 'hybrid medicine', its benefits and possible side effects are taken as being similar to those of the reference medicine.

For the full list of all side effects reported with Potassium Chloride Solution for Infusion, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

Why was Potassium Chloride Solution for Infusion approved?
The MHRA decided that the benefits of Potassium Chloride Solution for Infusion outweigh the identified risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Potassium Chloride Solution for Infusion?
A risk management plan (RMP) has been developed to ensure that Potassium Chloride Solution for Infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Potassium Chloride Solution for Infusion including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Potassium Chloride Solution for Infusion
A Marketing Authorisation was granted in the UK on 7 November 2017.

The full PAR for Potassium Chloride Solution for Infusion follows this summary.

For more information about treatment with Potassium Chloride Solution for Infusion, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2018.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Potassium Chloride Solution for Infusion (PL 40739/0044) could be approved. The product is a prescription only medicine (POM) used:

- as a source of the potassium cation for the treatment or prevention of potassium depletion in patients for whom dietary measures or oral medication are inadequate or in critical care settings in which patients are often fluid restricted and regular monitoring of serum potassium levels and ECG are regularly monitored.
- for the treatment of severe hypokalaemia or diabetic ketoacidosis.

This medicine may also be used cautiously in those taking digoxin where potassium depletion may cause arrhythmias.

The application was submitted using the National Procedure. The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Potassium Chloride 15% w/v Concentrate for Solution for Infusion (Mercury Pharma International Limited) which was first licenced to Antigen International Limited on 1 December 1986. The reference product is currently held by Mercury Pharma International Limited (PL 02848/5917R).

Potassium is the major cation of intracellular fluid and is essential for maintenance of acid-base balance, isotonicity, and electrodynamic characteristics of the cell. The electrolyte is an important activator in many enzymatic reactions and is essential to a number of physiologic processes including transmission of nerve impulses, contraction of cardiac, smooth, and skeletal muscles, gastric secretion, renal function, tissue synthesis, carbohydrate utilisation and protein synthesis.

No new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a hybrid generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture and assembly of the product.

Scientific Advice had been provided by the MHRA to the applicant in 2013, which included guidance on the legal basis of the application and quality questions.

During assessment of the application, major objections were raised with respect to the quality and safety of the product. The application was considered by the Committee on Human Medicines (CHM) at their meeting in June 2017. In response to the CHM advice, the applicant provided additional data and detailed clarification of the points that had been raised. The information provided was adequate and the issues were resolved.

A Marketing Authorisation was granted in the UK on 7 November 2017.

II QUALITY ASPECTS

II.1 Introduction

Each ml of the solution for infusion contains 29.8 mg of potassium chloride. Each ml of this medicine contains 0.4 mmol of potassium and 0.4 mmol of chloride.

The finished product is presented as a ready to use sterile solution supplied in a polyolefin/styrene infusion bag which is sealed in an overwrap. The infusion bags are filled with 50ml or 100ml of solution. Each fill weight is supplied in cartons of 20 infusion bags.

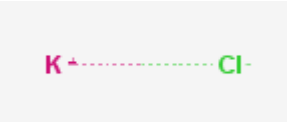
Each 50ml bag contains 20 mmol of potassium chloride.
Each 100ml bag contains 40 mmol of potassium chloride.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Potassium chloride
Chemical name: As above

Structural formula:



Molecular formula: KCl
Molecular weight: 74.5513
Appearance: White or almost white, crystalline powder or colourless crystals
Solubility: Freely soluble in water and practically insoluble in anhydrous ethanol

Potassium chloride is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, potassium chloride, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe and efficacious solution for infusion containing 0.4 mmol potassium chloride per ml that could be considered a hybrid medicinal product of Potassium chloride 15% w/v concentrate for solution for infusion (Mercury Pharma International Limited). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 9 months for the 50ml fill volume and 12 months for the 100ml fill volume with the storage conditions "Store the unopened bags in their overwrap. Protect from light and store at less than 25°C, do not freeze."; "Store in a separate location away from other IV infusion bags."; "Do not use if the overwrap or infusion bag is damaged or if the solution is cloudy or has particles in.". This product is for single use only, and once opened it should be used immediately.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application consists of a change in pharmaceutical form, strength and route of administration compared to the reference medicinal product.

Potassium Chloride 0.4 mmol/mL (3% w/v) Solution for Infusion is well established as a solution for infusion in many different clinical conditions where fluid and electrolyte losses can become a severe hazard for the patient. In the majority of cases it is not necessary to determine and replace individual deficits and solutions such as this product can be administered for supplementation.

Potassium chloride has a well-established clinical and toxicological profile.

As the pharmacodynamic, pharmacokinetic and toxicological properties of potassium chloride are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The Marketing Authorisation Holder's (MAH's) non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Potassium is the major cation of intracellular fluid and is essential for maintenance of acid-base balance, isotonicity, and electrodynamic characteristics of the cell. The electrolyte is an important activator in many enzymatic reactions and is essential to a number of physiologic processes including transmission of nerve impulses, contraction of cardiac, smooth, and skeletal muscles, gastric secretion, renal function, tissue synthesis, carbohydrate utilisation and protein synthesis.

The transmembrane electrical potential of most cells is determined by the ratio of intracellular to extracellular potassium concentration. In hyperkalaemia, an increase in the extracellular potassium concentration decreases the potential difference, which defines the resting potential of the cell. When the resting potential approaches threshold, the cell depolarises and may not be able to repolarise (repolarisation block), resulting in the cell being non-functional.

Hypokalaemia is when the extracellular potassium concentration decreases, causing the potential difference across the membrane to increase thereby increasing the stimulus required to bring about depolarisation (depolarisation block), causing the cell to be non-functional.

As both hyperkalaemia and hypokalaemia result in cells becoming non-functional, it is logical that some symptoms of both disorders are similar, i.e. weakness, lethargy, gastric hypomotility, cardiac arrhythmias, and conduction disturbances. Both can be life-threatening.

Furthermore, potassium, being the major intracellular ion, is the main determinant of intracellular ionic strength. Cellular ionic strength greatly influences cellular metabolism as evidenced by the marked clinical abnormalities attributable to cell overhydration or dehydration.

Chloride, the major extracellular anion, closely follows the physiologic disposition of sodium and also potassium and changes in the acid-base balance of the body are reflected by changes in serum chloride concentration.

The effects of an intravenous infusion of potassium chloride 0.2 mmol/L in normal saline were investigated in seven rabbits. Seven control rabbits received infusion of normal saline only. Administration of potassium chloride was found to potentiate skeletal muscle contraction and to reverse twitch fatigue. It was suggested that the effects were due to maintenance of intracellular potassium associated with inhibition of potassium efflux from skeletal muscle cells.

Potassium chloride elicits increased glucose utilisation in cells, possibly via an increase in intracellular sodium concentrations. High concentrations of potassium chloride depolarize cell membranes, leading to sodium influx via activated voltage-sensitive sodium channels.

Intracellular and extracellular levels of potassium are usually maintained within narrow limits. However, when potassium is administered as a drug, normal homeostatic mechanisms may not apply. Although exogenous administration of potassium may not significantly increase the total body content, there may be proportionally greater increases in extracellular concentrations, which could result in adverse effects.

For example, it is possible that rapid infusions of potassium chloride may increase the risk of hyperkalaemia and toxicity. A study was carried out to assess the effects of multiple, clinically relevant doses of potassium chloride (equivalent to 2 mmol/60 kg body weight) administered as rapid central or peripheral intravenous boluses to healthy anaesthetized pigs.

Aortic root potassium levels increased significantly following both routes of administration but the peak concentrations were higher and occurred significantly more rapidly after central administration. Changes in potassium levels in the aortic root showed an inverse correlation with cardiac output after central venous administration of potassium chloride but not after peripheral administration. Although marked transient hyperkalaemia occurred in all the pigs, no electrocardiographic evidence of hyperkalaemia could be demonstrated and it was concluded that small bolus doses of potassium chloride by peripheral or central intravenous injection were safe in normal, haemodynamically-stable pigs. The results are consistent with those of a small-scale study of rapid bolus injections of potassium chloride in humans.

The results of *in vivo* studies in Wistar rats indicate that potassium depletion is associated with marked increases in potassium tolerance and potassium clearance despite significant reductions in the concentration of skeletal muscle Na+/K+-ATPase, which is needed for muscular uptake of potassium. This suggests that the risk of potassium intoxication may not be increased during potassium repletion.

III.3 Pharmacokinetics

No new pharmacokinetic studies have been performed in support of this application because exogenous potassium and chloride would be expected to follow normal physiological pathways in the human body. These pathways are already well characterised and described in standard texts.

The proposed product is to be administered by intravenous infusion and will therefore show 100 % absorption. It is also known that orally administered potassium salts are readily absorbed from the gastrointestinal tract in humans. It is estimated that over 90 % of dietary potassium is absorbed from the gastrointestinal tract.

Potassium has a large volume of distribution in the human body. Active ion transport by the Na+/K+-ATPase carrier system ensures rapid transfer of potassium to intracellular fluid and tissues against the concentration gradient. Potassium is the most abundant intracellular cation. It is found primarily in muscle, and the normal intracellular content is 150-160 mmol/L, with modest variations between different types of cells.

The primary regulation of the body content of potassium occurs in the kidneys by glomerular filtration and tubular secretion in exchange for sodium or hydrogen ions under the influence of aldosterone and other factors such as sodium excretion, dietary potassium intake and plasma pH. Under conditions of normal intake, 10-20 % of the potassium filtered at the glomerulus is excreted, but fractional excretion of potassium can vary from 1 % when intake is restricted to over 100 % when intake is excessive. Nevertheless, the capacity of human kidneys to conserve potassium is generally poor and urinary excretion of potassium continues even under conditions of severe depletion. Under conditions of potassium deficiency, 10-50 mmol potassium may be excreted by the human kidneys each day.

The results of *in vivo* studies in Wistar rats indicate that potassium depletion is associated with marked increases in potassium tolerance and potassium clearance despite significant reductions in the concentration of skeletal muscle Na+/K+-ATPase, which is needed for muscular uptake of potassium. This suggests that the risk of potassium intoxication may not be increased during potassium repletion.

Overall, potassium undergoes approximately 90 % renal excretion, with the remainder excreted in the faeces and, to a lesser extent, in sweat and saliva. Under normal circumstances, potassium excretion in the faeces does not undergo homeostatic regulation, but amounts to only 5-15 mmol/day. When renal function is impaired both the absolute quantity and the proportion of potassium in the faeces are increased, but variation in renal excretion is usually the only method by which the body controls external potassium balance.

III.4 Toxicology

The addition of 3 % potassium chloride to the diet of Wistar rats for 18 months did not affect their clinical condition, acid-base balance or death rate. Standard haematological and clinical chemistry parameters were unaffected. However, feeding with potassium chloride did lead to growth retardation, increased water intake and increased urinary volumes. Serum potassium levels and urinary potassium excretion increased but there was no increase in serum chloride levels. Hypertrophy of the adrenal zona glomerulosa occurred, probably as a result of chronic stimulation of the adrenal cortex by the potassium.

Studies were carried out in rabbits to determine the effects of administering a 0.3 % potassium chloride infusion at full speed push in comparison with a 1 % potassium chloride infusion at a rate of 100 drips per minute. The mean lethal infusion time was significantly longer in the rabbits given the 0.3 % infusion. Serum concentrations of potassium increased but serum levels of sodium, calcium, chloride and bicarbonate decreased after the infusion. There was no statistically significant difference between the serum potassium levels attained in the two groups, nor were there any differences in the urinary volume or urinary concentration of any electrolyte between groups.

Looking at morphological changes, cardiac dilatation and congestion/stasis were observed in the animals that died following administration of the potassium. Ischaemic and hypoxic changes were seen in various organs. On microscopic and ultrastructural analysis, there was evidence of destruction of cardiac fibres, with thickening, concentrating or disappearing of the Z-line, constriction of glomerular capillaries, enlargement of the Bowman capsule, thinning and fusion of foot processes and apoptosis with phagocytosis in the brain. These effects were more pronounced in the rabbits given the 1 % potassium chloride solution.

High concentrations of potassium chloride can cause neuronal damage. Incubation of rat striatal neurons with high concentrations of potassium for 24 hours led to a significant reduction in the glucose content of the medium and a significant reduction in percentage cell viability. The results of further tests suggested that the lethal effects on cells were not dependent on increased sodium influx induced by the potassium.

The results of the studies presented above are generally consistent with the known effects of potassium chloride. The safety profile potassium is very well established from knowledge of its physiological effects and long-term clinical experience with oral and parenteral potassium chloride products. It was not therefore considered necessary to conduct further non-clinical toxicology studies.

Genotoxicity and carcinogenicity

In mutagenicity assays, potassium chloride gave a negative result in the Ames test and did not induce unscheduled DNA synthesis in HeLa S3 cells. However, a narrow range of high doses of potassium chloride did increase mutation frequency in Chinese hamster V79 cells. Chromosome aberrations were also induced in Chinese hamster ovary cells by high concentrations of potassium chloride, as expected from previous research. The aberrations observed included both deletions and exchange figures.

Solutions of both potassium chloride and sodium chloride were capable of inducing lethality and mutations when administered at very high 2M concentrations to logarithmic growth phase cells of the yeast *Saccharomyces cerevisiae*. The reversions included base substitutions and frameshift mutations. However, stationary-phase cells were not mutated and both potassium chloride and sodium chloride exhibited concentration-dependent anti-mutagenic effects in these cells.

In carcinogenicity studies, oral potassium chloride had a dose-dependent promoting effect on chemically-induced glandular stomach carcinogenesis in Wistar rats. A similar effect was seen with sodium chloride. Potassium chloride has also been shown to be a weak promotor of urinary bladder carcinogenesis in a rat model following exposure to a bladder tumour initiator. In a further study of the administration of potassium chloride in the diet of groups of 85 male and female Wistar rats for 4-130

weeks (without prior exposure to a bladder tumour initiator), potassium chloride was found to be only a weak tumour promotor, inducing only a few pre-neoplastic lesions of the urinary bladder epithelium of one male and one female rat.

In a later 30-month carcinogenicity study by the same group, 3 % dietary potassium chloride had only a slight effect on the early onset of oncolytic tubules in Wistar rats from 18 months of treatment. Only a slight increase in pre-neoplastic lesions was noted in the urinary bladder epithelium.

The use of low doses (comparable to dietary intake) of intravenous potassium chloride for the normalisation of serum potassium levels is considered unlikely to be associated with an increased risk of genotoxicity or carcinogenicity.

Reproductive and developmental toxicity
Potassium chloride has been reported to induce myometrial contractions in *in vitro* studies. High concentrations of 10-30 mM potassium chloride produced dose-related contractions of the uterus of Sprague Dawley rats, possibly by activating intracellular signal transduction mechanisms. Contractions of oestrogen-primed rat myometrium were also induced by 30, 60 or 90 mM solutions of potassium chloride. Suggested mechanisms included an effect on calcium influx or activation of other cellular processes by the potassium. Doses of 60 mmol potassium chloride have also be shown to induce contractions of the human umbilical artery and vein *in vitro*. These effects are unlikely to be clinically relevant in the case of intravenous infusions of potassium chloride for the correction of potassium deficiency in critical care situations.

No reports of teratogenic, embryotoxic or other reproductive toxic effects of potassium chloride in animals were retrieved from the published literature in a search of the Medline database from 1945 to date. Potassium and chloride ions are routinely ingested in the diet during pregnancy and lactation. The therapeutic use of potassium chloride for the normalisation of serum potassium levels is therefore considered unlikely to be associated with reproductive toxicity. The prescribing information for the proposed products will state that they should be used only if considered essential by the physician and should be administered under the supervision of the prescribing physician.

Local tolerance
High concentrations of potassium chloride can cause tissue irritation as discussed in the clinical overview. No non-clinical local tolerance studies were retrieved from the published literature. The central venous route of administration proposed in this application should avoid complications due to local intolerance.

Overall conclusion on toxicology
Potassium chloride has been extensively used clinically for a considerable period of time. The pharmacology, pharmacokinetics and toxicology of potassium chloride are considered to be well established. The applicant's review and summary of the toxicological data for potassium chloride is sufficiently detailed and adequate. No concerns have been raised with impurities in the drug substance and in the drug product. An acceptable justification for an absence of an environmental risk assessment is provided.

III.5 Ecotoxicity/environmental risk assessment (ERA)
As this product is intended for substitution with other products already on the market, no increase in environmental exposure is anticipated. An ERA is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

Intravenous infusions of potassium chloride are already routinely used for the prevention and treatment of potassium depletion in patients for whom oral treatment is not feasible. Products available for this purpose include 10 mL ampoules containing 15 % w/v concentrates (20 mmol potassium in 10 mL) for dilution with at least 500 ml suitable infusion fluid (to a final concentration of 0.04 mmol/mL or lower) prior to administration by slow intravenous infusion over 2-3 hours.

The main reason for dilution is the fact that high concentrations of potassium chloride can cause tissue irritation. Hence, when higher concentrations of potassium chloride are required, the central venous route of administration is recommended.

Until now there has been no licensed ready-to-use product, resulting in the use of unlicensed specials or the need for preparation of solutions for intravenous infusion by dilution of potassium chloride concentrates prior to use.

The proposed products will contain potassium chloride at a concentration of 0.4 mmol/mL whereas the reference product contains potassium chloride 2mmol/mL for dilution to a final concentration of 0.04 mmol/ml or lower.

The ready to use product is expected to reduce the risk of human errors and contamination. A low-volume product could be useful when high volumes of fluids are contraindicated.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of potassium chloride.

IV.2 Pharmacokinetics

In line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

The proposed products are to be administered by intravenous infusion and will therefore show 100 % absorption. It is also known that orally administered potassium salts are readily absorbed from the gastrointestinal tract in humans.

Potassium has a large volume of distribution in the human body. Active ion transport by the Na+/K+-ATPase carrier system ensures rapid transfer of potassium to intracellular fluid and tissues against the concentration gradient. Potassium is the most abundant intracellular cation. It is found primarily in muscle, and the normal intracellular content is 150-160 mmol/L, with modest variations between different types of cells.

The primary regulation of the body content of potassium occurs in the kidneys by glomerular filtration and tubular secretion in exchange for sodium or hydrogen ions under the influence of aldosterone and other factors such as sodium excretion, dietary potassium intake and plasma pH.

Overall, potassium undergoes approximately 90 % renal excretion, with the remainder excreted in the faeces and, to a lesser extent, in sweat and saliva. When renal function is impaired both the absolute quantity and the proportion of potassium in the faeces are increased, but variation in renal excretion is usually the only method by which the body controls external potassium balance.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

Slow intravenous infusions of Potassium Chloride IV administrations at a rate not exceeding 20 mmol potassium per hour using an infusion pump is standard practice and a well-established therapy for the correction of electrolytes imbalances. No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application; a review of published studies follows.

Clinical studies in adults

Results were presented from a retrospective study that reviewed the records from 5 months of hospital admissions to the Intensive Care unit in Detroit. The study evaluated the administration of 495 sets of potassium chloride infusions. Each set consisted of 1-8 consecutive individual infusions of potassium chloride 20 mmol in 100 mL saline over one hour via central or peripheral veins. The Authors concluded that *"When indicated, potassium can be administered in the intensive care unit setting with relative safety as intravenous infusion of 20 mEq of potassium chloride in 100mL normal saline given in 1 hour…. Further prospective and controlled studies are warranted to better define the plasma pharmacokinetic and cardiac electrophysiological effect of concentrated potassium infusion"*

This retrospective study looked at potassium concentrations of 20mmol in 100ml which is half the concentration of the proposed product. Although no major events of concern were noticed, the Authors suggested the need of further studies with high concentrated potassium infusions. The above study cannot be considered supportive for this application.

In another study forty critically ill Intensive Care unit adult patients with hypokalaemia were treated with infusions containing 20 mmol potassium chloride in 100 mL normal saline over one hour. A total of 26 patients received the infusion via a central vein and 14 via a peripheral vein. The infusions were well tolerated and were not associated with transient hyperkalaemia. Continuous ECG monitoring showed no arrhythmias, changes in cardiac conduction intervals or other changes. This study assessed patients' responses to 20mmol of potassium chloride in 100mL of normal saline which is half the concentration of the proposed product. Therefore, this study cannot be considered supportive for this application.

A study of different doses and concentrations of potassium chloride infusions were evaluated in 48 critical-care patients, aged 25-86 years. Twenty-six patients with serum potassium levels of 3.2-3.5 mmol/L received potassium chloride 20 mmol in 100 ml normal saline over one hour. Eleven patients with serum potassium levels of 3.0-3.2 mmol/L were given potassium chloride 30 mmol in 100 ml normal saline over one hour and a further 11 patients with serum potassium below 3 mmol/L received potassium chloride 40 mmol in 100 ml normal saline over one hour. Serum potassium was checked before, at 30 minutes, and at the end of the infusion.

Some patients received furosemide within 6 hours of entering the study. The group receiving the 40mmol potassium chloride tended to be younger and required more catecholamine and antidysrhythmic therapy. In the 20mmol and 30mmol/L groups , one patient per group had a peak potassium of > 5.0 mmol/L at the completion of the infusion but was no treated and was asymptomatic. The 40mmol/L group had a pre-treatment potassium levels ranging from 2.1 to 3.1 mmol/L. The range of increase in the potassium levels was 2.4 to 4.4 mmol/L at 60 minutes.

The Authors concluded that potassium infusion ranging from 20 to 40 mmol in 100mL of normal saline over 1 hour could be given to patients with pre-treatment potassium level < 3.5mmol/L without evidence

of cardiovascular instability or compromise. Longer-term efficacy was not addressed by this study. The degree of change in potassium level was found to depend on the dosage given, whereas the absolute level achieved depended on both the dosage and the pre-treatment potassium levels.

Three different concentrations of Potassium chloride were assessed in this study. The 40mmol/L concentration was assessed in 11 patients with the lowest level of serum potassium pre-treatment (2.1 to 3.1mmol/L) and it was well tolerated. This study shows that concentrations of 40mmol/L in 100ml of saline given to patients with a very low pre-treatment serum potassium level are well tolerated. However, the number of patients is quite small to provide clinical conclusions and suggests that suitability of high potassium concentrations could be based on pre-treatment serum potassium levels.

In another study, the safety and efficacy of intravenous infusions of concentrated potassium chloride solutions using micro-pumps was evaluated in critically ill adolescent, adult and elderly patients with hypokalaemia. A total of 64 patients received a concentrated solution of potassium chloride 1208 mmol/L and 64 control patients received a standard concentration of 201 mmol/L. The hourly rate of administration of potassium chloride was the same in both groups. All the patients tolerated the concentrated infusion without evidence of haemodynamic changes, hyperkalaemia or acute cardiac dysfunction.

Only a brief abstract of this study was in English. The amount of saline used to dilute the potassium is not clear. The Authors concluded that it took about 15 hours and 14 hours for the 2 groups to correct the hypokalaemia. This is in contrast with the previous studies and may suggest that the 2 concentrations were strongly diluted. This study cannot be considered supportive for this application since the data are not available.

A small-scale study of bolus injections of potassium chloride 0.033 mmol/kg into a central vein before and after a cardiopulmonary bypass procedure in 10 adult and elderly subjects. Although significant hyperkalaemia (7-9 mmol/L) developed in both the aortic root and radial artery, there were no electrocardiographic or haemodynamic consequences in any patient, perhaps due to the transient nature of the hyperkalaemia.

The number of patients included in this study is quite small. Furthermore, the level of hyperkalaemia developed in the aortic root and radial artery is very high and although the patiients didn’t show any electrocardiographic/haemodynamic consequences this is still a reason for concern if this dose is administered to a wider population.

In a case study of a 74-year-old man who received a rapid bolus injection of potassium chloride 20mmol followed by additional 80mmol by combination of oral and intravenous doses over the next 2 hours for the treatment of hypokalemia with recurrent unstable ventricular tachycardia and multiple defibrillators with cardiomyopathy which resulted in immediate resolution without toxic effects.

A single case study with a patient with cardioverter-defibrillator is not considered supportive for this application

<u>Studies in children</u>
A retrospective review was presented of 794 intravenous administrations of potassium chloride in 211 children of median age 4 months (range 10 days – 18 years) at a mean dose of 0.97 mmol/kg. The Authors concluded that “IV KCL is an effective therapy for rapid correction of hypokalemia that can be safely administered in CICU patients. Used of standardised dosing protocols should be continued to prevent or reduce errors in dosing.”

The study discusses the usefulness and safety of IV KCL administration in a cardiac paediatric Intensive unit. The mean dose given to children was 0.97mmol/Kg. No discussion on the concentration of the formulation is provided and it is not possible to extrapolate the actual concentration given from the data provided. The study cannot be considered supportive for this application.

Results were presented from a study of 20 infants and children following intravenous infusions of concentrated solutions of potassium chloride (200 mmol/L) at a rate of 0.25 mmol/kg/hour. The selection criteria were a serum potassium level < 3.5mmol/L and presence of at least one ECG change (decrease amplitude of T waves, U waves and depressed ST segment). The Authors concluded that controlled infusion of concentrated solution of potassium chloride at a rate of 0.25mmol/Kg/hour is a safe and effective way to achieve rapid correction of hypokalemia with ECG changes using minimal fluid volumes. In the study, concentrations of potassium chloride of 200mmol/L were administered, which is half the concentration of the proposed product. Therefore, this study cannot be considered supportive for this application**.**

In another study 31 paediatric cardiac patients (mean age 19 ½ months) were studied to determine potassium dose-responses characteristics. The potassium chloride was given by syringe pump at a dose of 0.5 mmol/kg of 2 meq/mL (undiluted) over two hours for the correction of hypokalaemia following cardiac surgery in infants and children. The infusion was piggybacked into an existing line, central or peripheric. The infusion was repeated as necessary to achieve serum K >/= 4.0 meq/litre. Blood samples were collected at 15-30 min before and after KCL infusion. The mean dose administered was 0.72+/-0.23 meq/Kg. this produced a mean rise in serum K of 0.61+/-0.48meg/litre. Of 100 administrations, 11 resulted in no change or a decrease in serum K. Serum potassium levels greater than 5 mmol/L were seen in 4/100 cases. The Authors concluded that "intravenous KCL supplementation in a dose of 0.5 meq/Kg administered over 2 hours is safe and effective for paediatric postoperative cardiac patients. Serum K should be measured to monitor therapy, due to variable response".

The above study administered undiluted concentrations of potassium chloride (2 meq/mL) which is higher than the proposed concentration. The infusions were piggybacked into an existing central or peripheral line which could have diluted the original concentration. Forty of the infusions were accompanied by concomitant administration of either whole blood or packed cells. The study seems to support the safety use of concentrated potassium infusions. However, the way the infusion was administered (piggybacked to an existing line or accompanied by concomitant administration of whole blood or packed cells) could have affected the final concentration. This study alone cannot be considered supportive for the propose application.

Overall conclusions on clinical safety

Six studies in adults and 3 in children were submitted to support the use of the proposed formulation's concentration. However, out of the 9 studies only two one in adults and one in children, were conducted using the proposed concentration of 400mL/l . The other studies lacked details of administration information or used concentrations lower than the proposed one.

The two studies alone were considered to provide insufficient evidence to support the safety use of the highly concentrated product in clinical practice. Although the argument that a ready to use preparation will reduce the risk of error mistakes and contamination is supported, in consideration of the potential risk of cardiotoxicity with high concentrated administrations of potassium chloride, more data were required in order to provide reassurance that the 400mmol/L proposed formulation can be used safely in the proposed indications and population.

Very limited data from clinical studies using the 0.4mmol/ml proposed concentration are available. However, some of the UK Hospitals guidelines recommend this concentration for the treatment of severe hypokalemia in clinical care units only. Furthermore, the expert advice sought states: "having pre-mixed known concentrations of potassium an advantage that would decrease the margin for error

provided the required education, training and competencies are assured and the new higher concentrations to be confined to critical care areas (ICU, CCU, high dependency etc.). This would need coordination with NHS procurement and NHS Trusts as well as monitoring by NHS Improvement".

Overall, the new ready-to-use formulation could bring an advantage and reduce the risk of human errors. This formulation could also be useful in patients under fluid restrictions. Although very limited data from clinical trials are available, there is evidence for the use of the 40mg/100ml concentration in clinical practice for the treatment of severe hypokalaemia in intensive care units only where adequate cardiac monitoring and treatment of immediate potential serious consequences if given incorrectly is available.

The application was presented to the CHM in June 2017, where it was agreed that the application for a marketing authorisation was approvable from a clinical perspective, if it was made clearer that Potassium Chloride 0.4mmol/mL Solution for Infusion is for critical care situations only. The opening line of section 4.2 posology of the SmPC currently states "This product is only for use in clinical care situations". This is acceptable and satisfies the request of the CHM.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Potassium Chloride Solution for Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Hyperkalaemia
	Hyperchloraemia
	Cardiotoxicity
	Interactions that can cause increased potassium levels
	Interactions that can caused decreased potassium levels or decreased response to potassium chloride
	Interactions that can increase the risk of cardiotoxicity
Important potential risks	Adverse effects caused by incorrect route of administration or rate of infusion
Missing information	Use during pregnancy and breast-feeding

V.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

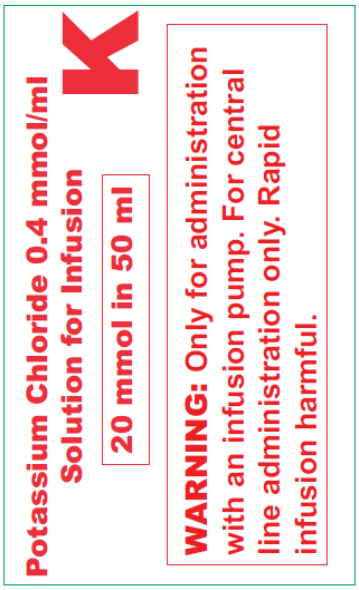
VI Overall conclusion, benefit/risk assessment and recommendation

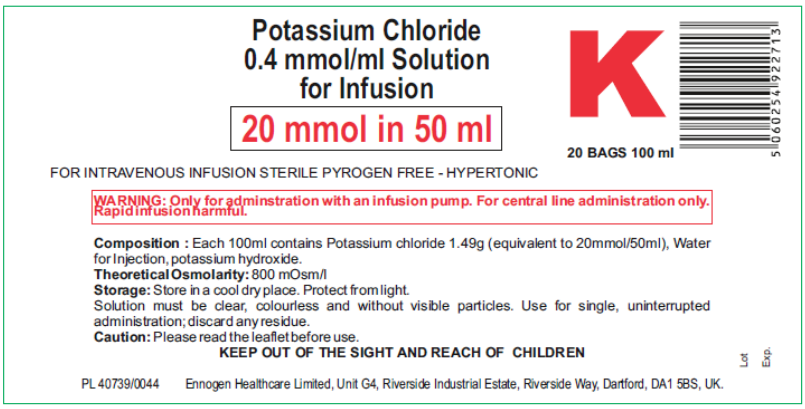
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with potassium chloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk balance is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

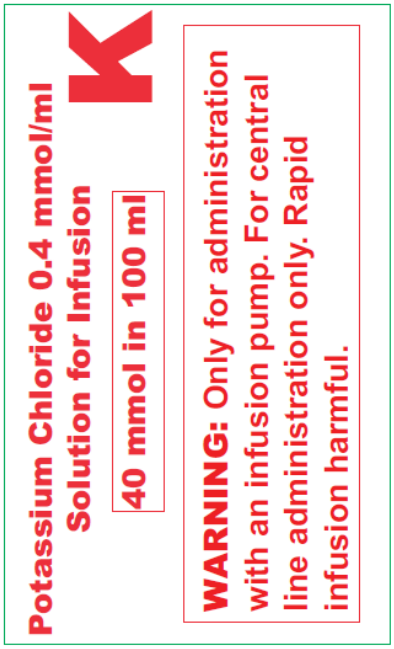
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Potassium Chloride 0.4mmol/mL Solution for Infusion is presented below






Potassium Chloride 0.4mmol/ml
Solution for Infusion
40 mmol in 100ml
SINGLE USE, STERILE IV INFUSION- HYPERTONIC
Formula per 100ml
Potassium chloride 2.98g
Water for Injection
Potassium hydroxide
mmol/100ml
Potassium 40
Chloride 40
WARNING: Only for administration with an infusion pump.
For central line administration only. Rapid infusion harmful.
Do not use unless solution is clear, without visible particles.
Read carefully the enclosed leaflet before use.
Keep out of sight and reach of children.
Store below 25°C. Do not freeze. Protect from light.
PL40739/0044
Ennogen Healthcare Ltd.
Unit G4 Riverside Ind. Estate
Riverside Way, Dartford
DA1 5BS (UK)
5 060254 922683


Potassium Chloride 0.4 mmol/ml
Solution for Infusion
40 mmol in 100 ml
WARNING: Only for administration with an infusion pump. For central line administration only. Rapid infusion harmful.

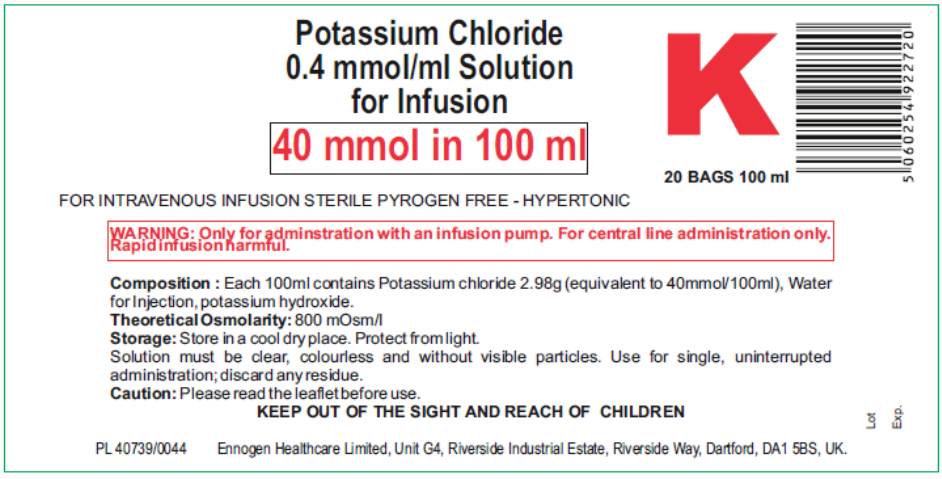

Potassium Chloride
0.4 mmol/ml Solution
for Infusion
40 mmol in 100 ml
20 BAGS 100 ml
5 060254 922720
FOR INTRAVENOUS INFUSION STERILE PYROGEN FREE - HYPERTONIC
WARNING: Only for adminstration with an infusion pump. For central line administration only. Rapid infusion harmful.
Composition : Each 100ml contains Potassium chloride 2.98g (equivalent to 40mmol/100ml), Water for Injection, potassium hydroxide.
Theoretical Osmolarity: 800 mOsm/l
Storage: Store in a cool dry place. Protect from light.
Solution must be clear, colourless and without visible particles. Use for single, uninterrupted administration; discard any residue.
Caution: Please read the leaflet before use.
KEEP OUT OF THE SIGHT AND REACH OF CHILDREN
Lot
Exp.
PL 40739/0044 Ennogen Healthcare Limited, Unit G4, Riverside Industrial Estate, Riverside Way, Dartford, DA1 5BS, UK.

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)